# Valproic acid use in psychiatry: issues in treating women of reproductive age

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Valproic acid, a well known anticonvulsant, is being used by psychiatrists increasingly to manage bipolar and other affective disorders. Because of the demographics of the population affected by such psychiatric conditions, more women of childbearing age are likely to be exposed to this teratogenic drug. Neural tube defects (NTD) are the most common of the major anomalies associated with in utero valproic acid exposure, and are estimated to occur in 1% to 2% of exposed fetuses. Other teratogenic effects include facial dysmorphism, congenital cardiac defects, limb reduction defects and other skeletal anomalies.

Prenatal diagnosis, in particular maternal serum α-fetoprotein screening and targeted ultrasonography, should be offered to all pregnant women exposed to valproic acid and couples need to be aware of the prenatal diagnostic options available to them. Periconceptual prophylaxis with high doses of folic acid is recommended for all women on valproic acid and counselling should also emphasize planning pregnancy to optimize folic acid supplementation. Psychiatrists should be aware of the teratogenic potential of valproic acid and know how to counsel their patients of reproductive age.

Les psychiatres utilisent de plus en plus l'acide valproïque, anticonvulsivant bien connu, pour gérer des troubles bipolaires et d'autres troubles de l'affectivité. À cause de la démographie de la population touchée par ces troubles psychiatriques, plus de femmes en âge de procréer sont susceptibles d'être exposées à ce médicament tératogène. Les malformations du tube neural (MTN) sont les plus fréquentes des principales anomalies associées à une exposition à l'acide valproïque in utero et l'on estime que de 1 à 2 % des fœtus exposés sont atteints. Ce médicament a d'autres effets tératogènes comme la dysmorphie du visage, les malformations cardiaques congénitales, l'atrophie des membres et d'autres anomalies squelettiques.

Il faudrait offrir à toutes les femmes enceintes exposées à l'acide valproïque de se soumettre à un diagnostic prénatal, et en particulier à un dépistage des α-fétoprotéines dans le sérum de la mère et à une échographie ciblée. Les couples doivent connaître les possibilités de diagnostic prénatal qui sont disponibles. On recommande une prophylaxie périconceptuelle à forte dose d'acide folique pour toutes les femmes qui prennent de l'acide valproïque et les conseils devraient aussi mettre l'accent sur la planification de la grossesse de façon à optimiser l'utilisation des suppléments d'acide folique. Les psychiatres devraient connaître le potentiel tératogène de l'acide valproïque et savoir quels conseils donner à leurs patientes en âge de procréer.

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Medical subject headings: abnormalities, drug induced; alpha-fetoproteins; neural tube defects; valproic acid

*J Psychiatry Neurosci* 1998;23(4):223–8.

Submitted Dec. 12, 1997
Revised Mar. 24, 1998
Accepted Apr. 2, 1998

Valproic acid, a well-established anticonvulsant drug, is being used increasingly to manage conditions other than epilepsy, particularly bipolar and other affective disorders. Because of the demographics of the population affected by such psychiatric conditions, more women of childbearing age are likely to be exposed to this teratogenic drug.

Neurologists, family physicians and obstetricians who treat women with epilepsy have recently become aware of the teratogenic risks of the anticonvulsants (particularly valproic acid and carbamazepine) that their patients are taking, and are being educated about the appropriate management and counselling of women of childbearing age with epilepsy. It is therefore timely that psychiatrists, who are prescribing valproic acid more often for their patients with mood disorders, also become informed about this drug's teratogenic potential so that they can counsel and advise their patients appropriately.

Motherisk is a consultation service in Toronto for women concerned about antenatal exposure to drugs, chemicals and radiation. Between April 1994 and January 1997, 62 women were booked into the Motherisk clinic to discuss the use of valproic acid during pregnancy. Of these 62 women, 16 were taking the drug for psychiatric disorders. The use of valproic acid to treat bipolar affective disorder has increased recently; 9 of the 12 patients taking valproic acid for bipolar disorder seen at the clinic began treatment after August 1995. This may reflect the changing prescribing practice of local psychiatrists.

## Background

Valproic acid is an anticonvulsant drug that was first licensed for use in 1978. It was used primarily for the treatment of absence seizures but has been shown to be effective in a wide range of both partial and generalized seizure disorders. Valproic acid produces effects on isolated neurons in a manner similar to 2 other commonly used anticonvulsant drugs — phenytoin and ethosuximide. At therapeutic concentrations, the drug acts predominantly by limiting sustained repetitive neuronal firing through voltage- and use-dependent blockade of sodium channels, although it is likely that there are other mechanisms involved.

### *Indications*

For the past 25 years, lithium has been the primary treatment for both the acute and prophylactic management of bipolar affective disorder and its efficacy is well established. However up to 40% of patients taking lithium fail to respond to the drug. Furthermore, some patients cannot tolerate lithium because of a number of adverse effects, which include gastrointestinal disturbances, weight gain, skin rashes, tremor and cognitive problems. Some of the potential longer-term adverse effects of lithium are thyroid and renal dysfunction.[1] In part because of its toxic effects, it is estimated that between 25% and 50% of patients do not comply with their treatment and thus may be at increased risk of relapse.[2] Other studies have shown that the presence of subsyndromal manic or depressive symptoms are also risk factors for relapse.[3]

Because of poor tolerability or incomplete symptom control associated with by the long-term use of lithium, alternative therapies have been sought and the best established of these are the anticonvulsant agents carbamazepine and valproic acid.

### *Mechanism of action*

It has been postulated that the antipsychotic effects of valproic acid result from GABAergic mechanisms. Valproic acid does not modify neuronal responses to iontophoretically applied GABA, but it does increase the amount of GABA that can be recovered from the brain after administration to animals. In vitro, valproic acid has been shown to stimulate the activity of the GABA synthetic enzyme, glutamic acid decarboxylase, as well as to inhibit GABA degradative enzymes, GABA transaminase[4] and succinic semi-aldehyde dehydrogenase.[5] Although the increased levels of GABA have not been directly related to the drug's antiseizure activity, they may explain its antipsychotic effects.[6]

### *Dosage and effectiveness*

The doses established for the anticonvulsant effects of valproic acid are assumed to be appropriate for the treatment of patients with manic depression, although formal dose-response studies in such patients are lacking. Therefore dosing of valproic acid is adjusted to maintain plasma concentrations from 50 to 100μg/mL.[6]

In a double-blind, placebo-controlled study in 1983[7]

valproic acid was shown to result in marked improvement in a group of 5 patients with acute mania. In the same study it was also shown to have positively affected patients with bipolar affective or schizoaffective disorder, 8 out of 9 of whom had been unresponsive to lithium, demonstrating its prophylactic effect. There have also been several studies showing successful treatment of acute mania with carbamazepine, valproic acid, or both. It has been suggested that valproate may be the drug of choice in patients with rapid cycling, dysphoric mania and mixed states as well as those with schizoaffective and other atypical bipolar disorders.[8,9]

## Teratogenic effects

The first reports suggesting adverse outcomes in fetuses exposed to valproic acid were published in 1980,[10–12] and there have since been numerous publications concerning the incidence of both major and minor malformations in exposed infants. The first report linking valproic acid use by the mother with fetal neural tube defects (NTD) was published in 1982.[13]

### *Neural tube defects*

Neural tube defects are the most common of the major anomalies associated with in utero valproic acid exposure and are estimated to occur in 1% to 2% of exposed fetuses. It appears that valproic acid use is associated specifically with lumbosacral meningomyelocele rather than with other forms of NTD such as anencephaly,[14] with the ratio of meningomyelocele to anencephaly reported in 1 series of infants to be 33 to 1.[15] It has been postulated that valproic acid effects predominantly closure site 5 (the lumbosacral region) as well as influencing the process of canalization in forming the caudal end of the neural tube.[16] Of note, carbamazepine, the other anticonvulsant known to be associated with an increased risk of NTD, does not appear to preferentially effect closure sites 5 and 1, and cases of meroacranium, holoacranium and spina bifida cystica have all been reported in fetuses exposed to carbamazepine.[17]

In some cases, including the 2 cases reported in the review by Ardinger et al,[18] the defects are low-lying lumbosacral lesions and may be covered by skin.

### *Skeletal abnormalities*

Radial ray defects are relatively common birth defects and may occur in isolation or as components of multiple malformation syndromes. There have been several reports in humans[19–22] and animal data have shown limb reduction defects after exposure to valproic acid. Limb reduction defects have been induced in mice[23] and rabbits[24] exposed to valproic acid at crucial times of embryonic development.

Sharony et al[25] reported 2 cases of limb reduction defects associated with valproic acid exposure. One fetus had shortened upper and lower limbs as well as talipes and abnormal hand posture detected by routine ultrasonography at 20 weeks gestation. Other reported radial defects have included absent or triphalangeal thumb[20] and pre-axial polydactyly.[26]

The most commonly reported skeletal abnormalities associated with exposure to the drug are arachnodactyly with partly overlapping fingers and toes and hyperconvex fingernails.[19] An underriding third toe is also a commonly reported finding.[27]

Several sibling pairs with features of fetal valproate syndrome that have been reported were born to mothers on long-term valproate therapy, suggesting that associated genetic predisposition may play a role in the development of the phenotype.[28,29]

### *Craniofacial and other defects*

In 1984 DiLiberti et al[30] proposed that intrauterine exposure to valproic acid produces a consistent craniofacial phenotype that they called the fetal valproate syndrome. By this time there had already been several reports suggesting that in utero exposure to valproic acid could result in an unusual facial phenotype.[11,31,32] The typical facial features reported by DiLiberti et al included epicanthal folds, which continued in an inferior and lateral manner to form an infraorbital crease or groove, as well as a flattened nasal bridge, small upturned nose, long upper lip with relatively shallow philtrum, thin upper vermillion border and downturned angles of the mouth. They also reported associated problems such as congenital cardiac defects, cleft lip, hypospadias, strabismus, nystagmus, psychomotor delay, low birth weight and neural tube defects.

In 1988 Ardinger et al[18] evaluated 19 children who had in utero exposure to valproic acid, either as monotherapy (8 patients) or in combination with other anticonvulsants (11 patients). They found no consistent alterations of pre- or postnatal growth with expo-

sure to valproic acid monotherapy when these children were compared with those exposed to valproic acid polytherapy, two thirds of whom demonstrated postnatal growth deficiency and microcephaly. Craniofacial anomalies included mid-face hypoplasia, short nose with a bridge that was broad or flat or both, epicanthal folds, minor anomalies of the ear, philtrum or lip, and micrognathia. Many of these craniofacial anomalies are nonspecific and have been seen in infants exposed to other anticonvulsants.[33]

Cardiovascular abnormalities reported in association with in utero valproic acid exposure include coarctation of the aorta and interrupted aortic arch, hypoplastic left heart syndrome, aortic valve stenosis, ventricular septal defect and pulmonary atresia.[34] Major defects, such as tracheomalacia and talipes equinovarus, and minor anomalies, such as metopic ridging, outer orbital ridge deficiency and bifrontal narrowing, appear to be peculiar to infants exposed to valproic acid. Hydrocephalus in the absence of spina bifida has been reported in 2 patients exposed to valproic acid monotherapy.[35] Omphalocele has also been reported in at least 2 infants with other features typical of fetal valproate syndrome.[36]

*Neonatal effects*

Manifestations of withdrawal, including irritability, jitteriness, abnormal tone, feeding difficulties and seizures, have been described in infants whose mothers took valproic acid during pregnancy (especially high doses in the last trimester).[37] Other neonatal consequences of maternal valproic acid use include hyperbilirubinaemia, hepatotoxicity (which can be fatal), transient hyperglycinaemia and intrauterine growth retardation.

## Prenatal issues

Because NTD are the most common major malformations associated with valproic acid exposure, prenatal diagnosis is focused on their detection. The 2 main tools for prenatal detection of NTD are α-fetoprotein estimation and ultrasonography.

*α-fetoprotein*

α-fetoprotein is a glycoprotein produced initially by the yolk sac and then by the fetal liver and gastrointestinal tract. α-fetoprotein can be measured both in amniotic fluid as well as in maternal serum and is now used widely as a marker in prenatal maternal serum screening programs. In 1972, Brock and Sutcliffe[38] demonstrated that pregnancies affected with open (not skin-covered) NTD had high amniotic fluid α-fetoprotein levels. Because α-fetoprotein is detectable in maternal serum, these estimations can also be used as screening tests for the presence of open NTD.

*Targeted ultrasound*

Because skin-covered lesions may not be associated with raised α-fetoprotein levels, an accurate prenatal diagnosis of valproic acid–associated NTD may be difficult. Thus prenatal evaluation of the valproic acid–exposed fetus must include targeted ultrasound examination, particularly of the caudal spine, even in the presence of normal α-fetoprotein levels.[39–41]

The neurological deficit associated with such caudal lesions may be minimal with the main derangement being of bladder or bowel function, or both, so that those affected are likely to be ambulatory and are unlikely to develop hydrocephalus. This is one of the more subtle issues that must be highlighted when counselling an expectant mother.

*Amniocentesis*

Amniocentesis may be offered to women as a somewhat more accurate measure of α-fetoprotein than maternal serum testing, although clearly there are increased risks associated with an invasive procedure. Generally, amniocentesis is used when a satisfactory ultrasound examination is not possible, for example in extremely obese women. Another method for detecting NTD is to measure amniotic fluid acetylcholinesterase (AChE), a somewhat more specific marker for NTD than α-fetoprotein.[42] In cases where the maternal serum α-fetoprotein level is elevated and ultrasound examination is normal, amniocentesis may be offered for a more definitive diagnosis of NTD, measuring amniotic fluid α-fetoprotein and AChE.

*Folic acid prophylaxis*

Prophylaxis with 5 mg of folic acid daily is recom-

mended for all women planning a pregnancy and who are taking valproic acid (or carbamazepine). Despite the negative animal studies and the absence of studies on humans showing that folic acid protects the embryo against the toxic effects of valproic acid and specifically NTD, current clinical practice is still to recommend periconceptional supplementation with a high dose (4 to 5 mg) of folic acid. Concerns have been raised in the past that folic acid, particularly in large doses, may decrease the absorption of zinc from the gastrointestinal tract and that this may have serious clinical consequences because zinc deficiency in animals has been reported to cause malformations, particularly of the central nervous system.[43] Dietary supplementation with 10 to 20 times the daily requirement of folic acid in rodents failed to decrease the toxic effects of valproic acid on the embryo and had no effect on zinc levels in the mother's liver, brain or kidney or in embryonic tissues.[44]

Ideally folic acid should be taken periconceptually so that it is being taken at the critical time of neural tube closure (up to 5 weeks after conception). Thus women taking valproic acid should be counselled and strongly encouraged to plan their pregnancies so that they are taking folic acid once they stop using contraception.

### *Genetics of bipolar disorder*

As part of the overall counselling process it is also important to discuss the genetics and likelihood of transmission of bipolar affective disorder. In a review of the literature, Rice et al[45] found that the likelihood of a first-degree relative of a patient with bipolar disorder also having bipolar disorder was in the range of 1.5% to 10.2%. The mean among the studies was 5.8%, which is consistent with most empiric recurrence risks. However, the likelihood of a first-degree relative of a person with bipolar disorder having any form of affective disorder is between 15% and 20%.[46,47]

Various subgroups of patients, for example those with a younger age of onset, appear to have a greater chance of transmitting bipolar disorder to their offspring than those with the rapid-cycling form of the condition.

### *Fetal risks of other major drugs for manic depression*

As with valproic acid, the 2 other major drugs used to treat manic depressive disorders are also teratogenic in humans. Carbamazepine has been shown to cause NTD in an estimated 1% of fetuses exposed during organogenesis.[48] This rate is about half of the risk associated with valproic acid. Lithium has been shown to increase the risk for the rare Ebstein anomaly involving the tricuspid valve.[49] The estimated rate of this malformation is in the range of 1%.

## Conclusions

Valproic acid is a drug that is being used increasingly to treat psychiatric disorders. Appropriate counselling regarding its potential teratogenic effects and optimal prenatal investigation and prevention strategies are important to ensure fetal well being.

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